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Treatment with Pimobendan is associated with an increased risk of arrhythmias in human heart disease patients. Is there any evidence that this is also true in dogs?

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Introduction

Pimobendan is a positive inotrope and balanced vasodilator via its actions as a calcium sensitiser and phosphodiesterase III inhibitor, respectively (1). Treatment of congestive heart failure (CHF) with pimobendan is supported by strong evidence in dogs, with multiple clinical trials demonstrating a resultant increase in survival time (2-5). However, the use of pimobendan for treatment of heart disease in human patients has been associated with increased risk of arrhythmias (6). This effect is attributed to the racemic nature of pimobendan resulting in (+) and (-) chiral enantiomers with the l-optical isomer having a significantly greater calcium sensitising effect (7-9). However, limited data are available regarding any effect of treatment with pimobendan on risk of arrhythmias in dogs. The aim of this knowledge summary is to analyse the available data to determine whether evidenced-based conclusions can be drawn.

The question

In [dogs with cardiac disease] does treatment with [Pimobendan] compared to [alternative treatments OR placebo] lead to [increased risk of arrhythmias]?

Search strategy

CAB Abstracts on Ovid (1973-2018 Week 20)

Date of Search = 31/05/2018

Exp Dogs/ OR (dog*.mp OR canine*.mp or canid*.mp)

AND

(Pimobendan.mp OR Vetmedin.mp)

AND

Exp arrhythmias/ or (arrhythmias.mp or arrhythmia.mp or dysrhythmia.mp)

Number of results from CAB Abstracts =19

Medline on Ovid (1946-2018)

Date of Search = 31/05/2018

Knowledge Summary: Treatment with pimobendan is associated with an increased risk of arrhythmias in human heart disease patients. Is there any evidence that this is also true in dogs?

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Dogs/ OR (dog*.mp OR canine*.mp OR canid*.mp)

AND

(Pimobendan.mp OR Vetmedin.mp)

AND

Exp Arrhythmias, Cardiac/ OR (arrhythmia.mp or arrhythmis.mp or dysrhythmia.mp)

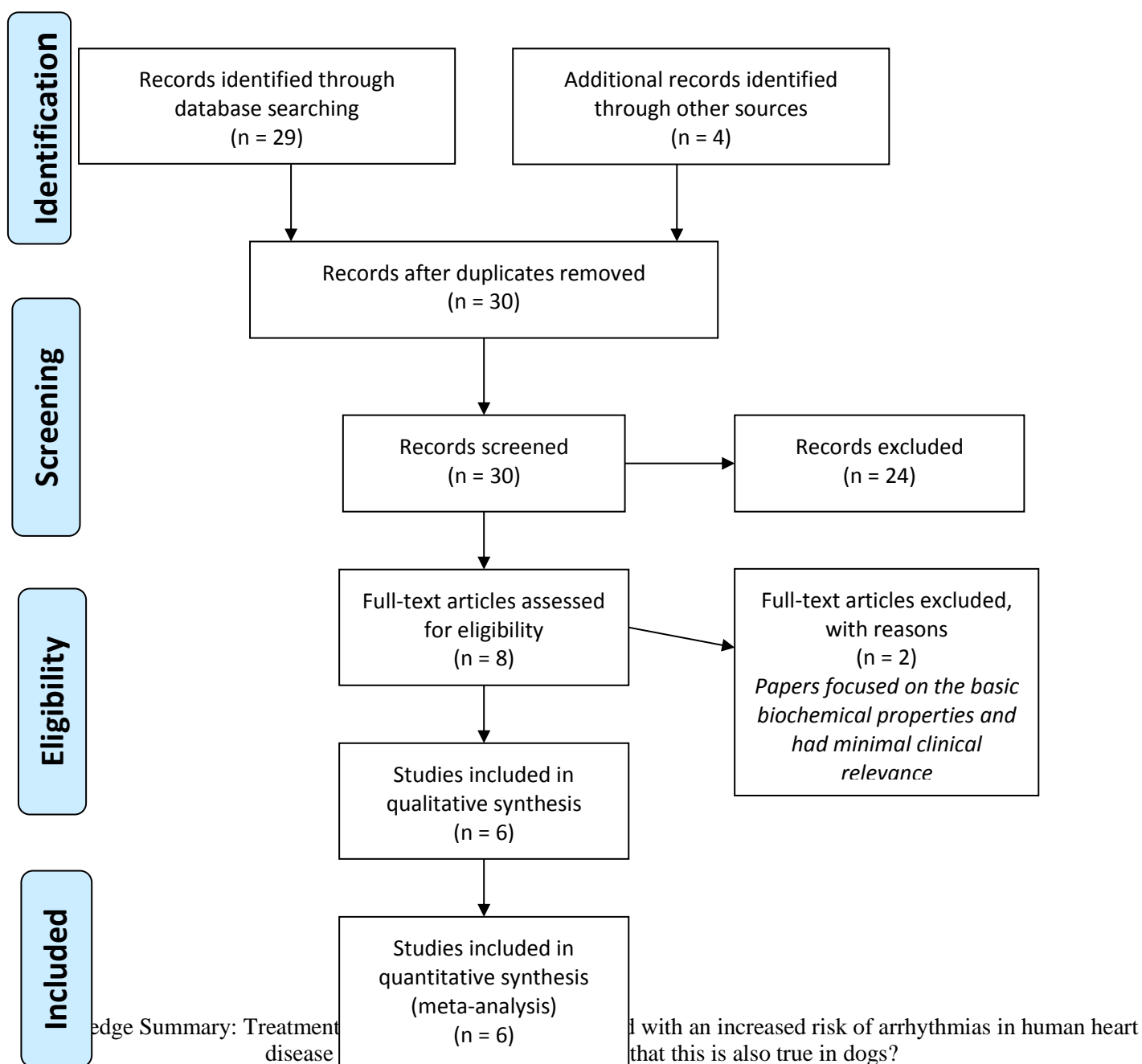
Number of results from Medline = 10

Given the small number of studies identified using our search strategy we searched the bibliographies of the relevant papers to identify other studies relevant to our question.

Search results



PRISMA 2009 Flow Diagram



Search last performed

31/05/2018

SUMMARY OF EVIDENCE

Paper 1: Effect of pimobendan on the incidence of arrhythmias in small breed dogs with myxomatous mitral valve degeneration (MMVD) (10)

Patient group: Eight client-owned small breed dogs (<15kg) with CHF due to MMVD

Study type: Prospective double-blind randomised placebo-controlled crossover study design

Outcomes: Average heart rate and incidence of arrhythmia, determined using 24 hour Holter electrocardiographic (ECG) analysis, was compared two weeks post administration of placebo or pimobendan to baseline data. A quality of life questionnaire was completed and sleeping respiration rates recorded by owners at baseline and two weeks post drug administration.

Key results: Quality of life scores were significantly improved following administration of both placebo and pimobendan ($p=0.021$ and $p<0.001$ respectively). No significant differences were identified in type or incidence of supraventricular or ventricular arrhythmia. Average heart rate with pimobendan was significantly lower than baseline ($p<0.001$) as was sleeping respiratory rate ($p=0.004$), which was also significantly different from placebo ($p=0.045$).

Study weaknesses: While key results were significantly different between treatment groups it must be noted that the small study size resulted in the study being underpowered for some tests. The effect of pimobendan was also only assessed in small breed dogs <15kg and so conclusions can only be applied to this subject group. Furthermore, only dogs with stable, medically controlled CHF due to MMVD were included, thus it could not be concluded the treatment with pimobendan would not result in arrhythmias in earlier stages of MMVD or in other cardiac diseases. CHF was identified on thoracic radiography which, although generally agreed as gold standard in veterinary medicine, can be subjective. Additionally, heart rate and rhythm was only recorded for 24 hours using the Holter ECG monitor, which might be insufficient to detect all arrhythmias that may be present. Finally, administration of pimobendan for two weeks may not be long enough for the drug to have a proarrhythmic effect.

Paper 2: Effects of the positive inotropic agents milrinone and pimobendan on the development of lethal ischaemic arrhythmias in conscious dogs with recent myocardial infarction (11)

Patient group: 36 male or female mixed breed dogs with experimentally induced myocardial infarction. Potential study animals underwent electrical stimulation to assess for a predisposition to develop arrhythmias, only those animals nonresponsive were entered into the study as they were considered 'low risk' for the development of subsequent lethal ischaemic arrhythmias were selected

Study type: Prospective, randomised, placebo- controlled study design

Outcomes: Electrophysiological testing and programmed ventricular stimulation at set time points post drug administration. Relevant parameters measured included: ECG intervals, minimum voltage required to produce a conducted ventricular impulse and incidence of ischaemic mortality at 24 hours post development of posterolateral myocardial ischaemia.

Key results: Administration of pimobendan postinfarction results in significant shortening of PR and QTc intervals ($p=0.01$ and $p=0.05$ respectively) as well as generalized shortening of refractory periods (p values ranged from 0.01 to 0.04 depending on the exact measurement site.) All placebo and pimobendan treated animals remained nonresponsive to programmed ventricular stimulation at all time points. One pimobendan treated animal was however excluded due to the postdrug appearance of spontaneous ventricular ectopy. No spontaneous or provoked ventricular ectopy was observed in the remaining pimobendan treated animals. Pimobendan administration resulted in a significant increase in the incidence of sudden ischaemic ventricular fibrillation, however incidence of ischaemic mortality at 24 hours was not significant ($p=0.083$) when compared to the low risk control group.

Study weaknesses: This study was carried out on dogs with experimentally-induced myocardial infarction, a condition rarely seen in dogs. Furthermore, a dose of 300µg/kg pimobendan administered IV over 20 minutes and a 200µg/kg/hour dose of milrinone administered via continuous intravenous infusion for 6 hours were used. These regimes were selected due to their ability to produce significant and sustained increased in cardiac inotropic status; there was no attempt to recreate therapeutic dosing schedules used for clinical canine heart failure patients.

Knowledge Summary: Treatment with pimobendan is associated with an increased risk of arrhythmias in human heart disease patients. Is there any evidence that this is also true in dogs?

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Paper 3: Effect of pimobendan or benazepril hydrochloride on survival times in dogs with congestive heart failure caused by naturally occurring myxomatous mitral valve disease: the QUEST study (4)

Patient group: Two hundred and sixty client-owned dogs recruited from 28 centres in Europe, Canada, and Australia

Study type: Prospective multicentre, single-blinded, positive-controlled study

Outcomes: The primary endpoint was a composite of cardiac death, euthanasia as a result of heart failure or treatment failure. The onset of arrhythmias was assessed at 1, 3, 6, 9, 12, 15 and 18 months using ECG.

Key results: The time to endpoint was 267 days for pimobendan and 140 days for benazepril. Hazard ratio = 0.688, 95% confidence limits = 0.516- 0.916, $p=0.0099$. This benefit persisted after adjustment for baseline variables. There was no difference in the onset of arrhythmias between the two treatment groups.

Study weaknesses: Only dogs with CHF as a result of MMVD were included. The primary endpoint was a composite of three possible outcomes (only two resulting in death), the third (treatment failure) lacks the incontrovertible nature of death and is yet to be validated as a good surrogate for survival, however the study outlines what was predefined as treatment failure. Treatment failure was used as a surrogate in 20 pimobendan and 27 benazepril dogs. Lack of double blinding meant that owners were aware of the medication used. Defining cause of death as cardiac or non-cardiac in an aging population is problematic due to comorbidity. Study population had a larger proportion of Cavalier King Charles Spaniels and Dachshunds than previous large trials. The primary parameter assessed was treatment efficacy, therefore the study was not designed specifically to detect arrhythmias, although ECGs were performed at multiple time points throughout the study and onset of arrhythmias recorded.

Paper 4: Efficacy of pimobendan in the prevention of congestive heart failure or sudden death in Doberman pinschers with preclinical dilated cardiomyopathy (DCM) (The Protect Study) (5)

Patient group: 76 client owned Dobermans at 10 centres in the UK and North America

Study type: Randomised, double blinded, placebo-controlled, parallel-group multicentre study

Outcomes: Primary endpoint was composite of onset of CHF or sudden death, secondary endpoint was death by any cause.

Key results: No significant difference between the proportion of dogs reaching the end-point in the pimobendan versus the placebo group ($p=.1$). Median time to primary end-point was significantly longer in pimobendan group (718 days, interquartile range 151-641 days) versus the placebo group (441 days, IQR 151-641 days) ($p=0.0088$). Median survival time was also significantly longer in pimobendan group (623 days, IQR 491-1531 days) versus the placebo group (466 days, IQR 236-710 days) ($p=0.034$). The primary end-point was reached earlier in dogs with higher heart rates and those with >4 VPCs on a 3 minute ECG. No increased risk of proarrhythmia or sudden death was associated with use of pimobendan ($P = 0.30$).

Study weakness: Only DCM in Dobermans was studied. A significant number of Dobermans with preclinical DCM develop arrhythmias, which may result in sudden death. Dogs with arrhythmias prior to treatment were noted in the study but not excluded. The study protocol was amended during recruitment to include hypothyroid dogs. Antiarrhythmic therapy was permitted if dogs developed ventricular arrhythmias during the trial, and these dogs remained in the study. Physical examinations were only performed every 6 months.

Paper 5: Effect of pimobendan in dogs with preclinical myxomatous mitral valve disease and cardiomegaly: EPIC study (12)

Patient group: 360 client-owned dogs with MMVD with left atrial-to-aortic ratio >1.6 , normalized left ventricular internal diameter in diastole >1.7 , and vertebral heart sum >10.5

Study type: Prospective, randomised, placebo-controlled, double blinded, multicentre clinical trial

Outcomes: Time to a composite of the onset of CHF, cardiac-related death, or euthanasia.

Key results: Median time to primary endpoint was 1228 days in the pimobendan group and 277 days in the placebo group ($P = 0.0038$). Hazard ratio for pimobendan group was 0.64 compared with the placebo group ($P = 0.0002$). There was no difference in adverse events between treatment groups ($P = 0.82$).

Study weaknesses: This study only assessed the effects of pimobendan in dogs with MMVD. Dogs under 6 years old and those <4.1 and >15 kg were excluded. While adverse events were noted and reported the study did not specifically investigate the incidence of arrhythmias; it is therefore possible that their presence was missed.

Knowledge Summary: Treatment with pimobendan is associated with an increased risk of arrhythmias in human heart disease patients. Is there any evidence that this is also true in dogs?

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Additionally, the summary of adverse events reported does not specifically list 'arrhythmia' and instead lists 'tachycardia' and further, a large proportion of the adverse events are categorised as 'other' (124/196).

Paper 6: Longitudinal Analysis of Quality of Life, Clinical, Radiographic, Echocardiographic, and Laboratory Variables in Dogs with Preclinical Myxomatous Mitral Valve Disease Receiving Pimobendan or Placebo: The EPIC Study (13)

Patient group: Three hundred and fifty-four dogs with MMVD and cardiomegaly

Study type: Prospective, double blinded study with dogs randomized (ratio 1:1) to pimobendan or placebo

Outcomes: Clinical, laboratory, and heart size variables in both groups were measured and compared at different time points and over the study duration. Relationships between short-term changes in echocardiographic variables and time to CHF and cardiac related death (CRD) were explored.

Key results: Heart size reduced in the pimobendan group compared to placebo ($P = <0.0001$): this reduction was associated with an increased time to CHF and CRD; hazard ratio for a 0.1 increase in normalized left ventricular internal diameter in diastole was 1.26 ($P = 0.0003$), hazard ratio for a 0.1 increase in left atrial-to-aortic ratio was 1.14 ($P = 0.0002$).

Study weaknesses: The study population included dogs >6 years old, body weight ($>4.1\text{kg}$ and $<15\text{kg}$) with advanced MMVD. Dogs with known clinically important systemic or other organ related disease were excluded, thus the study conclusions cannot be applied to a systemically unwell population. Furthermore, the study was designed to investigate the effect of pimobendan on the time to CHF not arrhythmias. However, auscultation performed throughout the study might have detected the occurrence of arrhythmias, and adverse events related to arrhythmias are not reported.

Comments

Paper one was the only paper to specifically investigate the incidence of arrhythmias in animals treated with pimobendan. While this study is a useful starting point the small study population ($n=8$) and the inclusion of only small-breed dogs with stable, medically-controlled CHF limits the generalisability of its findings. The merits of paper two were the larger study population combined with the assessment of electrophysiological parameters such as the voltage required to produce a ventricular impulse as an indicator of arrhythmic properties. However, the study was conducted on dogs with experimentally induced myocardial infarction, a proarrhythmic model, making it impossible to draw accurate comparisons to non-ischaemic conditions such as MMVD. Furthermore, dogs in this study were administered pimobendan doses chosen to induce increased cardiac inotropic status. It can therefore be concluded that the finding of increased ventricular fibrillation in this study is not clinically relevant. The QUEST, PROTECT and both EPIC studies were the largest and best designed. While none specifically aimed to collect data on occurrence of arrhythmias, the QUEST study found no increase in the onset of arrhythmia and the PROTECT study found no increased risk of proarrhythmia. Disappointingly neither EPIC study specifically reports arrhythmias as an adverse event however the first does report no overall difference in adverse events between the two study groups.

Clinical bottom line

To date there is no evidence to suggest Pimobendan is associated with an increased risk of arrhythmias in dogs.

REFLECTION/COMMENTS: The studies varied in quality and strength of evidence. Only two studies specifically investigated arrhythmia, one very small and the other carried out in an experimentally induced proarrhythmic disease model using non-therapeutic doses of pimobendan. The much larger EPIC study reported equal incidence of adverse events while the PROTECT and QUEST study specifically noted no increase in arrhythmias in patient groups treated with pimobendan. These studies were well designed and included a large and varied population of dogs, they therefore provide good quality evidence to support our clinical bottom line.

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Knowledge Summary overview

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